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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: NORMAN K. SPROCH DOCKET NO.: 0268P0342

SERIAL NO.: 09/287,307 EXAMINER: THAI PHAN

FILED: 04/07/1999 ART UNIT: 2123

TITLE: METHOD FOR THE CHARACTERIZATION OF THE THREE-DIMENSIONAL STRUCTURE OF PROTEINS EMPLOYING MASS SPECTROMETRIC ANALYSIS AND COMPUTATIONAL FEEDBACK MODELING

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

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CERTIFICATE OF MAILING

I hereby certify that on the 16th day of March, 2005, this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to: Mail Stop Appeal Brief-Patents, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

By: Alice B. Vanicek
Alice B. Vanicek

RENEWED REQUEST FOR REINSTATEMENT OF APPEAL AND TRANSMITTAL OF SECOND SUPPLEMENTAL BRIEF ON APPEAL

Dear Sir:

Pursuant to the provisions of 37 C.F.R. 1.192 and 1.193, the appellant hereby renews his request for reinstatement of the appeal and submits herewith three (3) copies of a Second Supplemental Brief on Appeal in the above-captioned patent application.

No fee for this request is believed to be due. Should there be any unforeseen cost, please charge any cost associated with the filing of this Supplemental Brief on Appeal to our Deposit Account No. 17-0055.

Respectfully submitted,

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APPELLANT'S SECOND SUPPLEMENTAL BRIEF ON APPEAL

(1) Real Party in Interest

The inventor, Norman K. Sproch, is the real party in interest in this case.

(2) Related Appeals and Interferences

No other appeals or interferences are known to appellant or to the appellant's legal representative that would have any bearing on the Board's decision in this appeal.

(3) Status of Claims

The present application is a Continuation-In-Part of U.S. Patent Application Ser. No. 08/569,358, filed on December 08, 1995, now abandoned.

Claims 1-18 are pending. All claims stand rejected under 35 U.S.C. §103(a) as obvious in view of Agrafiotis et al., U.S. Patent No. 6,434,490. The rejection of all pending claims is being appealed.

Previously, all claims were rejected under 35 U.S.C. §103(a) as obvious in view of Fuerstenau et al., U.S. Patent No. 5,770,857. The Examiner had also, apparently, further rejected claim 7 in view of the combination of Fuerstenau et al. and U.S. Patent Application Publication No. 2002/0150926 by Jindal.

Before that, all claims were finally rejected under 35 U.S.C. §102(e) as anticipated by Dunkel, U.S. Patent No. 5,572,125.

The applicant appealed the rejections based on the Dunkel reference through the timely filing of a Notice of Appeal on May 29, 2003, and a Brief on Appeal on August 13, 2003. Instead of filing an Answer and Reply Brief, the Examiner withdrew the finality of the rejections and issued a new ground of rejection in an Office Action mailed November 05, 2003, paper number 16. In response, the applicant submitted a Request for Reinstatement of Appeal and Supplementary

Brief distinguishing the Fuerstenau et al. and Jindal references on February 02, 2004. Again, the Examiner withdrew his rejections and issued a new Office Action dated January 19, 2005, citing Agrafiotis et al. Thus, the appellant renews his Request for Reinstatement of Appeal and is filing this Second Supplementary Brief to distinguish the Agrafiotis et al. reference.

Insomuch as the Examiner states in his latest Office Action that the rejections under Fuerstenau et al. and Jindal are moot, it is presumed that the present application has been found to be patentable over these references. Thus, while this Second Supplemental Brief incorporates the Brief on Appeal and [First] Supplemental Brief by reference, only the new ground for rejection is addressed herein.

(4) Status of Amendments

No amendment was submitted after the final rejection of all claims in 2003 that resulted in this appeal, nor has any amendment been submitted since.

(5) Summary of Invention

The invention is a method for characterizing the three-dimensional structure of a large molecule (e.g., a protein molecule) comprising (1) mixing a small molecule with a large molecule (large and small molecules are defined on page 18, lines 9-19) so that the small molecule binds non-covalently to the large molecule to form a large molecule-small molecule complex (pages 35-37; Figs. 8-11), (2) performing electrospray ionization mass spectrometry (ES-MS) to obtain the spectrum of the large molecule-small molecule complex (page 19, line 21 through page 34; Figs.

1-7; for additional background on ES-MS, see U.S. Patent 5,504,327), (3) repeating the first two steps with additional different small molecules (pages 35-37; Figs. 17A-17C), and (4) using the spectrum so obtained to characterize the three-dimensional structure of the large molecule (pages 38-45).

In one preferred embodiment, ES-MS data is used to calculate the binding constant (K_B) for the binding of the small molecule to the large molecule (pages 38-45; Fig. 21), the aforementioned mixing and ES-MS steps are repeated with additional different small molecules and the heat of formation (ΔHf) for the binding of each of the small molecules to a selected residue on the surface of the large molecule is calculated (pages 41-43), the heat of formation (ΔHf) for the binding of the small molecules to other selected residues on the surface of the large molecule is calculated (pages 41-45), the experimentally determined binding constant (K_B) is compared with the calculated heats of formation (Δhf)(pages 43-45), and these comparisons are used to characterize the three-dimensional structure of the protein (pages 43-45). The three-dimensional molecular model elucidated through these comparisons can then further refined using experimental/computational feedback modeling (page 51, line 11 through page 55 ; Fig. 22).

(6) <u>Issues</u>

Whether Claims 1-18 were properly rejected under 35 U.S.C. Sec. 103(a) as obvious in view of Agrafiotis et al.

(7) Grouping of Claims

The appellant believes that all claims should stand or fall together with respect to the prior-art rejection.

(8) Argument Against Rejection of Claims 1-18 Under 35 U.S.C. Sec. 103(a)

The applicant respectfully submits that none of the limitations of claims 1-18 are met or suggested by the Agrafiotis et al. patent.

The Examiner describes Agrafiotis et al. as teaching "a method and system with feature limitations substantially similar to the claimed invention," in that Agrafiotis et al. describe "mixing molecules to form a mixed solution of complex molecules for analysis...performing mass spectrometry analysis techniques...repeating the procedure...and using the spectral data to characterize the properties of the complex molecule compound structures" (pages 2-3 of Office Action).

In contrast, as recited in claim 1, the present invention comprises:

(a) mixing a small molecule with a large molecule so that the small molecule binds non-covalently to the large molecule to form a large molecule-small molecule complex;
(b) performing electrospray ionization mass spectrometry to obtain the spectrum of the large molecule-small molecule complex;
(c) repeating steps (a)-(b) with additional different small molecules; and
(d) utilizing the spectra obtained in steps (a)-(c) to characterize the three-dimensional structure of the large molecule.

Looking first at step (a), there is no disclosure or suggestion in Agrafiotis et al. to mix a small molecule with a large molecule so that they non-covalently bind to form a complex. As pointed out in the appellant's previous submissions, a "complex molecule" is not the same thing as a "molecule complex." Furthermore, the terms "small molecule," large molecule," "covalently," and "complex" do not appear anywhere in Agrafiotis et al.'s specification. Thus, it is unknown how the step limitation of "mixing a small molecule with a large molecule so that the small molecule binds non-covalently to the large molecule to form a large molecule-small molecule complex" can be found by the Examiner. Similarly, none of the other method steps (b)-(d) (which all involve a non-covalently bound large molecule/small molecule complex) are found in this reference.

Instead, Agrafiotis et al.'s invention is directed to a computer-based system and method for automatically generating chemical entities with desired physical, chemical and/or biological properties with respect to the production of drug leads. These combinatorial chemistry synthesis systems and methods have absolutely nothing to do with characterizing the three-dimensional structure of a large molecule as claimed by the appellant.

Moreover, the Examiner's reliance on "knowledge of a practitioner in the art" rather than a second reference to make the leap from Agrafiotis et al.'s patent to the present invention is baffling. The appellant can think of no way (and the Examiner provides no explanation) for how one skilled in the art would have found Agrafiotis et al.'s method or system to enable the practice of the claimed method steps of the present invention.

In summary, unlike the claims of the present application, there is no disclosure or suggestion in Agrafiotis et al. of a method that elucidates the three-dimensional structure of macromolecules, proteins, DNA, or RNA based on spectrometry of molecular complexes resulting from the non-covalent interaction of a large molecule with a small molecule.

In view of the foregoing, the appellant respectfully submits that all pending claims recite allowable subject matter. Accordingly, the appellant believes that the Examiner erred in rejecting the claims and urges the Board to so hold.

Should the Examiner disagree with the appellant's position as outlined above, the appellant respectfully requests that the appeal be forwarded to the Board for resolution. In the alternative, a telephonic interview with the Examiner and the Supervisory Patent Examiner under MPEP 1002.02(d)(2) is respectfully requested prior to any further re-opening of prosecution.

Respectfully submitted,

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(9) Appendix

The claims involved in this appeal read as follows:

1. A method for characterizing the three-dimensional structure of a large molecule comprising the steps of:

(a) mixing a small molecule with a large molecule so that the small molecule binds non-covalently to the large molecule to form a large molecule-small molecule complex;

(b) performing electrospray ionization mass spectrometry to obtain the spectrum of the large molecule-small molecule complex;

(c) repeating steps (a)-(b) with additional different small molecules; and

(d) utilizing the spectra obtained in steps (a)-(c) to characterize the three-dimensional structure of the large molecule.

2. The large molecule characterization method of Claim 1, wherein the three-dimensional structure characterization of step (d) is carried out by feedback modeling according to the following steps:

(e) providing data processing means;

(f) providing data storage means;

(g) digitizing raw experimental data acquired according to steps (a)-(c);

(h) storing the digitized data in said data storage means;

(i) initializing and running a selected computer program on said data processing means for simulating the experiment performed in steps (a)-(c);

(j) comparing simulation data obtained from step (i) with the digitized data from the experiment performed in step (g);

(k) if the comparing step (j) produces a result outside a predetermined parameter, establishing a feedback loop and initiating an iterative subroutine whereby the computer simulation adjusts itself, in an incremental way, to fit the simulation to the experimental value, compares the result to the experiment after each computational step and feeds the experimental data back into the input loop of the computation until the result of the comparison of step (j) is within the predetermined parameter.

3. The large molecule characterization method of Claim 1, wherein the large molecule is selected from the group consisting of polypeptides, proteins, DNA, RNA, oligosaccharides, and polymers thereof.

4. The large molecule characterization method of Claim 1, wherein the small molecules include crown ethers, macrocyclic polyethers, cryptands, and/or polymers of these compounds, or any other suitable ligand or macrocyclic ligand.

5. The large molecule characterization method of Claim 2, wherein the large molecule is selected from the group consisting of polypeptides, proteins, DNA, RNA, oligosaccharides, and polymers thereof.

6. The large molecule characterization method of Claim 2, wherein the small molecules include crown ethers, macrocyclic polyethers, cryptands, and/or polymers of these compounds, or any other suitable ligand or macrocyclic ligand.

7. A method for characterizing the three-dimensional structure of a large molecule comprising the steps of:

(a) mixing a small molecule with a large molecule so that the small molecule binds non-covalently to the large molecule to form a large molecule-small molecule complex;

(b) performing electrospray ionization mass spectrometry to obtain the spectrum of the large molecule-small molecule complex;

(c) using the spectrum from step (b) to calculate the binding constant K_B for the binding of the small molecule complex;

(d) repeating steps (a)-(c) with additional different small molecules;

(e) calculating the heat of formation (ΔH_f) for the binding of each of the small molecules used in steps (a)-(d) to a selected residue on the large molecule;

(f) repeating step (e) for other selected residues on the large molecule;

(g) comparing the binding constants (K_B) calculated in steps (c) and (d) with the ΔH_f values calculated in steps (e) and (f); and

(h) utilizing the comparisons of step (g) to characterize the three-dimensional structure of the large molecule.

8. The large molecule characterization method of Claim 7, wherein said comparing step (g) is carried out by feedback modeling according to the following steps:

(i) providing data processing means;

(j) providing data storage means;

(k) digitizing raw experimental data acquired according to steps (a)-(d);

(l) storing the digitized data in said data storage means;

(m) initializing and running a selected computer program on said data processing means for simulating the three-dimensional structure of said large molecule according calculations performed in steps (e)-(f);

(n) comparing simulation data obtained from step (m) with the digitized data from the experiment performed in step (k);

(o) if the comparing step (n) produces a result outside a predetermined parameter, establishing a feedback loop and initiating an iterative subroutine whereby the computer simulation adjusts itself, in an incremental way, to fit the simulation to the experimental value, compares the result to the experiment after each computational step and feeds the experimental data back into the input loop of the computation until the result of the comparison of step (n) is within the predetermined parameter.

9. The large molecule characterization method of Claim 7, wherein the comparisons of step (g) are utilized to identify the residue or residues on the surface of the protein molecule to which the small molecule is bound.

10. The large molecule characterization method of Claim 7, wherein the large molecule is selected from the group consisting of polypeptides, proteins, DNA, RNA, oligosaccharides, and polymers thereof.

11. The large molecule characterization method of Claim 7, wherein the small molecules include crown ethers, macrocyclic polyethers, cryptands, and/or polymers of these compounds, or any other suitable ligand or macrocyclic ligand.

12. The large molecule characterization method of Claim 8, wherein the large molecule is selected from the group consisting of polypeptides, proteins, DNA, RNA, oligosaccharides, and polymers thereof.

13. The large molecule characterization method of Claim 8, wherein the small molecules include crown ethers, macrocyclic polyethers, cryptands, and/or polymers of these compounds, or any other suitable ligand or macrocyclic ligand.

14. The large molecule characterization method of Claim 9, wherein the large molecule is selected from the group consisting of polypeptides, proteins, DNA, RNA, oligosaccharides, and polymers thereof.

15. The large molecule characterization method of Claim 9, wherein the small molecules include crown ethers, macrocyclic polyethers, cryptands, and/or polymers of these compounds, or any other suitable ligand or macrocyclic ligand.

16. The large molecule characterization method of Claim 7, further comprising the step of using the heat of formation calculated in step (e) and calculating the heat of reaction (ΔHRXN) for the binding of each of the small molecules used in steps (a)-(d) to a selected residue on the large molecule.

17. The large molecule characterization method of Claim 16, wherein the large molecule is selected from the group consisting of polypeptides, proteins, DNA, RNA, oligosaccharides, and polymers thereof.

18. The large molecule characterization method of Claim 16, wherein the small molecules include crown ethers, macrocyclic polyethers, cryptands, and/or polymers of these compounds, or any other suitable ligand or macrocyclic ligand.